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Case Report
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Granulomatous Interstitial Nephritis as the Presentation of Systemic Sarcoidosis

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Abstract

Sarcoidosis is a systemic disease rarely presenting with isolated renal involvement. In about a quarter of cases interstitial granulomatous nephritis develops, which can only be detected by a renal biopsy.

We present the case of a woman who came to our observation because of moderate renal failure with slight urine abnormalities (proteinuria 0.3 g/day, few hyalo-granular casts in the urinary sediment) and no systemic symptoms. Renal biopsy showed giant cell granulomas and infiltration of the renal interstitium by small lymphocytes and plasma cells. The following examinations allowed us to diagnose renal and extrarenal sarcoidosis.

Introduction

Sarcoidosis is a systemic disease rarely presenting with isolated renal involvement. The aetiology is unknown, but environmental factors such as infections may trigger the disease in people with a genetic predisposition [1].

Sarcoidosis has a benign course in up to two-thirds of cases; in one-third achronic disorder develops leading to organ impairment [2,3].

We present the case of a woman who came to our observation because of reduced renal function and slight urine abnormalities. The following work-up revealed renal and extrarenal sarcoidosis.

Case Presentation

A 53 year-old woman was found to have altered parameters of renal function (Serum Creatinine-SCr- 1.9 mg/dl) and anemia (hemoglobin -Hb- 10 g/dl) during a work-up fora 2-month period of asthenia that appeared a flu-like episode.

She reported no relevant elements in her clinical history besides frequent tonsillitis in her childhood. An occasional examination in 2007 showed SCr 0.6 mg/dl.

After some tests which confirmed the anomalies, she was admitted into our department. Physical examination was normal besides elevated blood pressure (150/100 mmHg).

The examinations performed showed SCr 2.3 mg/dl, Hb 9.8 g/dl, urine test: hematuria (5 Red Blood Cells/hmf), several hyalo-granular casts; proteinuria was 0.15-0.3 g/24 h (albuminuria 30 mg/24 h).

Other tests were: sodium 137 mEq/l, potassium 4.3 mEq/l, calcium 9.6 mg/dl, phosphorous 3.1 mg/dl, hemoglobin 10 g/dl, white blood cells 6500/mm^3 with normal formula, platelets 225000/mm^3, transferrin saturation 12%, reticulocytes 17.3%, total proteins 7.3 g/dl, gammaglobulins 23%, IgG 1519 mg/dl, IgA 294 mg/dl, IgM 97 mg/dl, slight metabolic acidosis (bicarbonate 22 mmol/l), high anti-streptolysin titre (466 UI/ml), C Reactive Protein (CRP) 3 mg/dl, Erythrocyte Sedimentation Rate (ESR) 78 mm/h.

Liver enzymes, LDH, haptoglobin, creatinekinase, bilirubin, blood glucose, uric acid, PT, PTT, folic acid and vitamin B12, Vitamin D, Hepatitis B antigen, HCV, HIV, ANCA, ANF, anti-DNA, anti-ENA, C3, C4, cryoglobulins, schizocytes were negative or within the normal range.

No monoclonal components were detected in the serum or in the urine.

Occult blood test in feces and urine culture were negative.

Ultrasound showed slightly hyperecogenic renal parenchyma and bilateral dilation of the right

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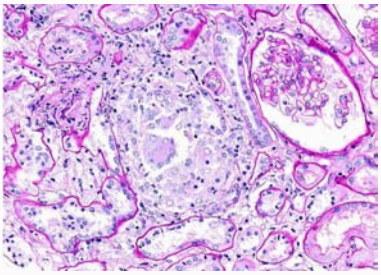

Figure 1: Renal biopsy. Giant cell granuloma in the renal interstitium (PAS stain, 200x).

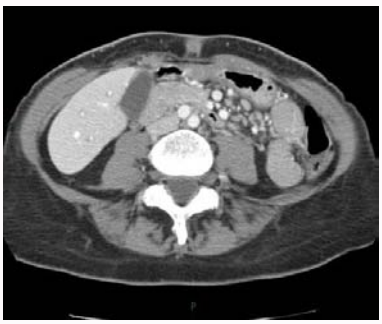

Figure 2: CT of the abdomen.Celiac, lomboaortic, interaortocaval, retrocrural and mesenteric lymph nodes of about 10 mm.

pyelocalyceal system; the bladder was normal. At echo-Doppler the renal arteries and veins didn't present stenosis or thrombosis. Dynamic renal scintigraphy with diuretic stimulation showed a non-obstructive stenosis of the uretero-pelvic junction.

Chest X-Ray, EKG, echocardiography and the ophtalmological examination were normal.

Renal biopsy was performed. Light microscopy showed 34 glomeruli, 4 of them with global sclerosis; the others had free urinary space, thin basement membranes, patent capillarylumina, thin mesangial axes. The interstitium was diffusely widened and infiltrated by small lymphocytes and rare plasma cells; some tubules were atrophic; multiple non-caseating non-necrotizing granulomas made by epithelioid giant cells (Figure 1) surrounded by small lymphocytes were found. These lesions were occasionally perivascular. At the immunohistochemical analysis some epithelioid elements and many lymphocytes resulted intensively positive for anti-FOXP3; no positive results were obtained for immunoglobulins or complement.

Due to the presence of interstitial granulomas, tuberculosis was searched: PPD skin test as well as Quantiferon test were negative; urine and sputum culture was negative for Koch bacillus. Molecular analysis for *M. tuberculosis, M. africanum, M. bovisin* the renal tissue resulted negative.

Serum Angiotensin Converting Enzyme was 54 UI/l (normal values 8-52).

At bronchoscopy no lesions were found. The Broncho-Alveolar Lavage (BAL)showed lymphocytes 20% and CD4/CD8 >1.

CT of the abdomen showed many celiac, lomboaortic, interaortocaval, retrocrural and mesenteric lymphnodes about 10 mm in size (Figure 2). At CT of the thorax 3 small nodules of about 5 mm were found in subpleural areas (Figure 3).

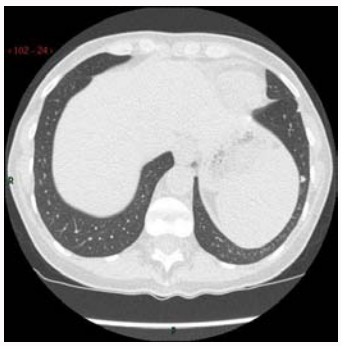

Figure 3: CT of the thorax. Nodule of about 5 mm in subpleural areas.

The patient was given prednisone 1 mg/kg/day for 7 days, followed by 0.5 mg/kg/day for 20 days, then 15 mg/day for one year.

After 3 months SCr was 1.2 mg/dl, Hb 12.3 g/dl, proteinuria 0.3 g/die, urinary sediment inactive, ESR 46 mm/h, CRP normal. One year later SCr was 1 mg/dl, Hb 13 g/dl, sACE 24 UI/l, proteinuria was absent, urinary sediment inactive, CT of the thorax and abdomen were normal.

Discussion

Our patient underwent a clinical work-up for moderate-degree renal failure without any significant abnormalities in the urine or in her clinical history except for a 2-month period of asthenia which occurred after a flu-like episode.

Renal biopsy showed the presence of non-caseating non-necrotizing giant cell granulomas in the interstitium and infiltration by small lymphocytes and plasma cells.

Tuberculosis was ruled out by Polymerase Chain Reaction on the renal tissue**.** Immunohistochemical analysis showed positivity for FOXP3, a marker expressed on Treg cells, which could support the hypothesis of sarcoidosis.

Other tests were carried out to confirm the diagnosis of sarcoidosis. CT revealed many lymph nodes in different areas of the abdomen and several small nodules in subpleural areas; BAL showed 20% lymphocytes and a CD4/CD8 ratio >1, which are both highly specific for sarcoidosis [4].

The patient was treated with corticosteroids resulting in complete regression of the renal and extrarenal manifestations which was evident after three months.

The organs that are most frequently involved in sarcoidosis are the lungs (90%), the skin (erythema nodosum) (24%), lymph nodes (15%), the eye (12%) and the liver (18%) [5]. The incidence of renal involvement in sarcoidosis ranges from 2 to 48% [6]. It may manifest with nephrocalcinosis, kidney stones, interstitial granulomatous nephritis, glomerulonephritis (focal segmental glomerulosclerosis, membranous glomerulonephritis -GN-, IgAGN, membranoproliferative GN, crescentic GN) and urinary obstruction by retroperitoneal lymph nodes [7].

A granulomatous infiltrate is found in the kidneys in 7% to 23% of cases, although it may remain clinically silent [8].

The involvement of sarcoidosis is rarely limited to the kidney [9-11] and even more rarely do the renal involvement and acute kidney injury represent the first manifestation of sarcoidosis [12-15].

Interstitial granulomatous nephritis represents 0.5 to 1.3% of the overall histologic findings. In these patients other causes of granulomatous forms must be ruled out, such as drugs (antibiotics, non-steroidal anti-inflammatory drugs, allopurinol, diuretics, proton pump inhibitors, cocaine) [16], infections (tuberculosis, histoplasmosis, brucellosis, toxoplasmosis, Epstein-Barr virus, Cytomegalovirus), vasculitis (granulomatous vasculitis-formerly Wegener-, esosinophilicvasculitis -Churg-Strauss-) and primary granulomatous interstitial disease.

Treatment of renal involvement in sarcoidosis is not standardized. Corticosteroids are usually given at 0.5 mg/kg/day - 1 mg/kg/day for 4 weeks, and then tapered until a daily dose of 5 mg to 10 mg is reached [16].

In conclusion, the role of renal biopsy in the presence of mild renal and clinical signs must be highlighted, as it might reveal interstitial nephritis leading to the diagnosis of a systemic disease.

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